Chromium(II)-catalyzed enantioselective arylation of ketones
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Abstract
The chromium-catalyzed enantioselective addition of carbo halides to carbonyl compounds is an important transformation in organic synthesis. However, the corresponding catalytic enantioselective arylation of ketones has not been reported to date. Herein, we report the first Cr-catalyzed enantioselective addition of aryl halides to both arylaliphatic and aliphatic ketones with high enantioselectivity in an intramolecular version, providing facile access to enantiopure tetrahydronaphthalen-1-ols and 2,3-dihydro-1H-inden-1-ols containing a tertiary alcohol.

Introduction
Catalytic enantioselective carbon–carbon bond formation reactions have achieved enormous development during the last few decades as a consequence of the growing demand for enantiopure compounds in modern industry, especially in the pharmaceutical industry. The chromium (Cr)-catalyzed enantioselective addition of carbo halides to carbonyl compounds is one of the most reliable methods in organic chemistry for chemoselective and structurally diverse synthesis [1-9]. To date, the Cr-catalyzed enantioselective carbonyl addition reactions mainly focused on allylation, propargylation, alkenylation and alkylation of aldehydes [10,11]. Since the first example of enantioselective alkylation of aldehydes catalyzed by a Cr(II)–salen complex in 1999 by Cozzi and co-workers [12], several elegant catalytic enantioselective alkylation and propargylation reactions have been developed by the groups of Nakada [13,14], Berkessel [15], Kishi [16], Sigman [17], Yamamoto [18], Guiry [19], Chen [20], Gade [21], White [22], and Zhang [23-25], respectively. The alkenylation and alkylation reactions were mainly explored by the Kishi group [26-30], and they established a toolbox approach to search for the specific ligand with a given substrate in the Cr-catalyzed process [28]. They successfully applied the method to the natural product total synthesis like halichondrin B and norhalichondrin B, and in the subsequent pharmaceutical study, finally leading to the discovery of the anticancer drug Eribulin [31-35]. However, to our knowledge, the Cr-catalyzed enantioselective arylation of carbonyl...
compounds has rarely been explored. On the other hand, most of the reactions focused on aldehyde components, while asymmetric addition to ketones remains a big challenge probably due to the decreased reactivity and selectivity [36,37]. A breakthrough was made by the Sigman group who reported the catalytic enantioselective addition of allylic bromides and propargyl halides toarylaliphatic ketones using oxazoline ligands with high enantioselectivity (up to 95% ee) [38-41]. After that, the Chen group also disclosed enantioselective alkylation of ketones using spirocyclic chiral borate and chiral bipyrindyl alcohol ligands with the ee value ranging from 27% to 97% [42,43]. However, as far as we know, a Cr-catalyzed enantioselective arylation of ketones has never been reported to date [44]. Tetrahydronaphthalen-1-ol bears a chiral tertiary alcohol center and is a common structural motif in numerous biologically active natural products and clinical drugs [45]. The method to prepare these compounds through intramolecular arylation of ketones would be highly desired. Herein, we report the first Cr-catalyzed enantioselective arylation of ketones in an intramolecular version.

Results and Discussion

Initially, the Cr-catalyzed asymmetric intramolecular arylation of arylaliphatic ketone 5-(2-iodophenyl)pentan-2-one (1a) was selected as the model reaction for optimization employing Kishi’s oxazoline/sulfonamides as the chiral ligands. A series of oxazoline/sulfonamide ligands (L1–L8) were tested and the results were summarized in Table 1. Four subgroups of R1 were studied (entries 1–4, Table 1) and isopropyl substituted oxazoline proved to be the best ligand with a 42% ee. Afterwards, R2 (Table 1, entries 2, 5 and 6) and R3 (Table 1, entries 6–8) substituents were also examined, and L8 bearing a methyl

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**Table 1:** Screening conditions of the catalytic enantioselective Cr-mediated arylation of ketone. 

<table>
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<tr>
<th>entry</th>
<th>L</th>
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<th>R3</th>
<th>Solvent</th>
<th>Yield (%)a</th>
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aYield of isolated product. bDetermined by HPLC analysis on a chiral column. cReaction at 0 °C for 24 h. dReaction at −20 °C for 24 h. eReaction at −40 °C for 24 h. fAryl bromide used instead of aryl iodide.
group in both R² and R³ gave the best enantiocontrol. The solvent effect was then investigated, and 1,2-dimethoxyethane (DME) was identified to be the best choice (Table 1, entries 8–10). Lowering the reaction temperature was found to be beneficial for improving the enantioselectivity, and when the reaction was performed at −20 °C, expected 2a was isolated in 81% yield with 97% ee (Table 1, entries 10–13). Aryl bromide proved to be an inferior coupling component, providing 2a in 35% yield and 70% ee (Table 1, entry 14).

With the optimized conditions in hand, the scope of the ketone component was first explored (Scheme 1). Aliphatic ketones with (longer) alkyl chain such as ethyl (1b) and n-hexyl ketones (1c), were also tolerated albeit with slightly decreased

![Scheme 1: Scope of the catalytic enantioselective Cr-mediated arylation of ketones.](image-url)
yield and selectivity. The asymmetric arylation of various arylaliphatic ketones also went smoothly (1d–h). Phenyl ketone 1d and ketones with electron-withdrawing groups in different substituent patterns gave the expected products with good enantiocontrol, while the enantioselectivity for ketone 1e bearing an electron-donating group decreased. The mild process exhibited excellent functional group tolerance, with chlorine (2f), fluoride (2g), and CF3 moieties (2h) well tolerated for further manipulation [46,47]. Heteroaryl ketones such as furan-substituted ketone (1i) were also suitable substrate, giving product 2i in 78% ee. The scope of the aryl halide component was next explored (1j–l). Aryl halides bearing different substituent patterns were tolerated giving the tetrahydronaphthalen-1-ols with good ee values. When 4-(2-iodophenyl)butan-2-one (1k) was used, enantiopure indan-1-ol was obtained in 70% yield and 82% ee.

Conclusion

In summary, we have developed the first Cr-catalyzed enantioselective arylation of ketones in an intramolecular version using oxazoline/sulfonamide L8 as the catalyst. Both aliphatic and arylaliphatic ketones proceeded smoothly, providing corresponding tetrahydronaphthalen-1-ols bearing a tertiary alcohol center with good enantioselectivities (up to 97% ee).

Experimental

General procedure for the chromium(II) catalyzed enantioselective arylation of ketones: The solution of L8 (0.25 equiv, 0.025 mmol) and CrCl2 (0.23 equiv, 0.023 mmol) in DME (1.0 mL) was stirred at room temperature in a glove-box for 1 h. Then the substrate 1 (1.0 equiv, 0.1 mmol), LiCl (2.0 equiv, 0.2 mmol), Mn powder (3.0 equiv, 0.3 mmol), NiCl2·DMP (0.12 equiv, 0.012 mmol) and Zr(Cp)2Cl2 (2.0 equiv, 0.2 mmol) were added successively and the mixture was stirred at indicated temperature for 24 h. After that, the mixture was filtered through a short pad of celite and purified by flash chromatography using silica gel or alumina (200–300 mesh) to give the product 2.

Supporting Information

Supporting Information File 1

Experimental File 1

Supporting Information File 1 Experimental procedures, analytical data for products, copies of NMR spectra and HPLC chromatograms.

References

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.275